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     FILE 'MEDLINE, CAPLUS, CANCERLIT, BIOSIS, EMBASE' ENTERED AT 12:49:22 ON
     13 MAR 2005
L1          8752 S CELECOXIB
L2            12 S EDOTECARIN
L3             0 S L1 AND L2
L4       3377225 NEOPLASIA OR CARCINOMA OR CANCER
L5             7 S L2 AND L4

=> s l1 and l4
L6          2241 L1 AND L4

=> duplicate remove l6
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, CANCERLIT, BIOSIS, EMBASE'
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PROCESSING COMPLETED FOR L6
L7          1509 DUPLICATE REMOVE L6 (732 DUPLICATES REMOVED)

=> d l7 and py<=1998
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     FILE 'MEDLINE, CAPLUS, CANCERLIT, BIOSIS, EMBASE' ENTERED AT 12:49:22 ON
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L1          8752 S CELECOXIB
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L5             7 S L2 AND L4
L6          2241 S L1 AND L4
L7          1509 DUPLICATE REMOVE L6 (732 DUPLICATES REMOVED)

=> s l7 and py<=1998
   2 FILES SEARCHED...
   4 FILES SEARCHED...
L8            17 L7 AND PY<=1998

=> d 1-17 bib abs

L8   ANSWER 1 OF 17     MEDLINE on STN
AN   1999052006     MEDLINE
DN   PubMed ID: 9834941
TI   Cancer chemoprevention. Part 1: Retinoids and carotenoids and
     other classic antioxidants.
AU   Singh D K; Lippman S M
CS   Department of Gynecologic Oncology, University of Texas, M. D. Anderson
     Cancer Center, Houston, USA.
SO   Oncology (Williston Park, N.Y.), (1998 Nov) 12 (11) 1643-53,
     1657-8; discussion 1659-60.  Ref: 111
     Journal code: 8712059. ISSN: 0890-9091.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
     General Review; (REVIEW)
     (REVIEW, TUTORIAL)
LA   English
FS   Priority Journals
EM   199902
ED   Entered STN: 19990316
     Last Updated on STN: 19990316
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Entered Medline: 19990226

AB **Cancer** chemoprevention is the use of specific natural or synthetic substances with the objective of reversing, suppressing, or preventing carcinogenic progression to invasive **cancer**. Currently, numerous chemopreventive agents are in various stages of development and testing. Part 1 of this two-part series provides an overview of issues unique to chemoprevention trials, including the use of surrogate biomarkers as end points. This is followed by a discussion of the retinoids, such as all-trans-retinoic acid (ATRA [Vesanoid]), 9-cis-retinoic acid (9cRA), and isotretinoin (Accutane), and the carotenoids (e.g., beta-carotene and lycopene) and other "classic" antioxidants (e.g., vitamins E and C and selenium). Research on these agents will be delineated by disease site when applicable. Part 2, which will appear in next month's issue, will focus on hormonally mediated chemopreventive agents, such as tamoxifen (Nolvadex), finasteride (Proscar), oral contraceptives, and dehydroepiandrosterone (DHEA). Part 2 also will cover nonantioxidant natural agents, such as calcium, the polyphenols, the isothiocyanates, and genistein; nonsteroidal anti-inflammatory drugs (NSAIDS), such as **celecoxib**, sulindac sulfone, and aspirin; difluromethylornithine (DFMO [Eflornithine]); oltipraz; and N-acetylcysteine.

L8 ANSWER 2 OF 17 MEDLINE on STN
AN 1998286828 MEDLINE
DN PubMed ID: 9625164
TI **Cancer** and arthritis share underlying processes.
AU Ziegler J
SO Journal of the National Cancer Institute, **(1998 Jun 3)** 90 (11) 802-3.
Journal code: 7503089. ISSN: 0027-8874.
CY United States
DT News Announcement
LA English
FS Priority Journals
EM 199806
ED Entered STN: 19980625
Last Updated on STN: 20000303
Entered Medline: 19980618

L8 ANSWER 3 OF 17 MEDLINE on STN
AN 1998117285 MEDLINE
DN PubMed ID: 9458081
TI Chemopreventive activity of **celecoxib**, a specific cyclooxygenase-2 inhibitor, against colon carcinogenesis.
AU Kawamori T; Rao C V; Seibert K; Reddy B S
CS Division of Nutritional Carcinogenesis, American Health Foundation, Valhalla, New York 10595, USA.
SO Cancer research, **(1998 Feb 1)** 58 (3) 409-12.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980306
Last Updated on STN: 20000303
Entered Medline: 19980224

AB Epidemiological and laboratory studies suggest that nonsteroidal antiinflammatory drugs reduce the risk of colon **cancer** and that the inhibition of colon carcinogenesis is mediated through modulation of prostaglandin production by cyclooxygenase (COX) isozymes (COX-1 and -2). Overexpression of COX-2 has been observed in colon tumors; therefore, specific inhibitors of COX-2 activity could potentially serve as chemopreventive agents. Our recent study indicated that **celecoxib** (SC-58635), a specific COX-2 inhibitor, suppressed colonic aberrant crypt foci formation induced by azoxymethane in rats and led us to investigate more specifically the chemopreventive potential of this compound using colon tumors as end points. Five-week-old male F344 rats were fed the

control diet (modified AIN-76A) or an experimental diet containing 1500 ppm **celecoxib**. Two weeks later, all animals except those in the saline-treated groups received s.c. injections of azoxymethane (15 mg/kg of body weight) once weekly for 2 weeks. All groups were kept on their regimen until the experiment was terminated, 50 weeks after carcinogen treatment. Colon tumors were evaluated histopathologically. Remarkably, dietary administration of **celecoxib** inhibited both incidence and multiplicity of colon tumors by about 93 and 97%, respectively. It also suppressed the overall colon tumor burden by more than 87%. The degree of tumor inhibition was more pronounced with **celecoxib** than it was with previously evaluated nonsteroidal anti-inflammatory drugs. The results of this study provide evidence, for the first time, that a specific COX-2 inhibitor, **celecoxib**, possesses strong chemopreventive activity against colon carcinogenesis.

L8 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:330637 CAPLUS
TI Selective cyclooxygenase-2 inhibitors: pharmacology, clinical effects and therapeutic potential
AU Van Ryn, Joanne; Pairet, Michel
CS General Pharmacology, Department of Biological Research, Dr Karl Thomae GmbH, Biberach, 88397, Germany
SO Expert Opinion on Investigational Drugs (**1997**), 6(5), 609-614
CODEN: EOIDER; ISSN: 0967-8298
PB Ashley Publications
DT Journal
LA English
AB Since the discovery of a second isoenzyme of cyclooxygenase, COX-2, the field of prostaglandin and inflammation research has rapidly developed. It is becoming more evident that inhibition of COX-2 results in the analgesic and anti-inflammatory actions of non-steroidal anti-inflammatory drugs (NSAIDs), and that inhibition of COX-1 results in the adverse side-effects seen with these compds. The mechanisms causing intestinal ulceration and renal toxicity are being elucidated, and large scale clin. trials with a preferential COX-2 inhibitor, meloxicam, and the first clin. results with highly selective COX-2 inhibitors, such as MK966 and **celecoxib**, support a superior benefit to risk ratio. In addition, important new areas where COX-2 expression is elevated, such as colonic **cancer**, have been identified and a role for COX-2 has also been proposed in Alzheimer's disease. Inhibition of COX-2 for these indications by selective COX-2 inhibitors may provide effective new therapies in the future.
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1999064337 EMBASE
TI The advent of highly selective inhibitors of cyclooxygenase - A review.
AU Cryer B.; Dubois A.
CS Dr. B. Cryer, Dallas VA Medical Center (111B1), 4500 S. Lancaster Road, Dallas, TX 75216, United States. bcryer@mednet.swmed.edu
SO Prostaglandins and Other Lipid Mediators, (1998) 56/5-6 (341-361).
Refs: 102
ISSN: 0090-6980 CODEN: POLMFL
PUI S 0090-6980(98)00064-1
CY United States
DT Journal; General Review
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Cyclooxygenase (COX) exists in two isoforms, COX-1 and COX-2. COX-1 is present and is constitutively expressed in most cells and tissues, whereas COX-2 is felt to principally mediate inflammation. However, this distinction appears to be challenged by recent observations. This review addresses the roles of COX-1 and COX-2 isoforms in physiologic and pathophysiologic states and reviews potential therapeutic roles for

selective COX inhibitors.

L8 ANSWER 6 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1999060732 EMBASE
TI Mechanism of action of antiinflammatory drugs.
AU Vane J.R.; Botting R.M.
CS J.R. Vane, William Harvey Research Institute, Royal London Sch. of Med./Dentistry, Queen Mary and Westfield College, Charterhouse Square, London ECIM 6BQ, United Kingdom
SO International Journal of Tissue Reactions, (1998) 20/1 (3-15).
Refs: 95
ISSN: 0250-0868 CODEN: IJTEDP
CY Switzerland
DT Journal; General Review
FS 037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB In 1971, Vane showed that nonsteroid antiinflammatory drugs (NSAIDs) inhibited the biosynthesis of prostaglandins and proposed this as their mechanism of action. Much work around the world has followed. The aspirin-like drugs inhibit the binding of the prostaglandin substrate, arachidonic acid, to the active site of the enzyme. After characterization of the COX-1 enzyme in 1976, a second COX gene was discovered in 1991 encoding for the inducible COX-2. The constitutive isoform of COX, COX-1, has clear physiological functions. The inducible isoform, COX-2, is induced by pro-inflammatory stimuli in migratory cells and inflamed tissues. The range of activities of NSAIDs against COX-1 compared to COX-2 explains the variations in the side effects of NSAIDs at their antiinflammatory doses. Drugs which have the highest potency on COX-2 and less effect on COX-1 will have potent antiinflammatory activity with fewer side effects. All the results published so far support the hypothesis that the unwanted side effects of NSAIDs, such as damage to the gastric mucosa and kidneys, are due to their ability to inhibit COX-1, while their antiinflammatory (therapeutic effects) are due to inhibition of COX-2. Other roles for COX-2 inhibitors will surely be found in the next few years, for prostaglandin formation is under strong control in organs such as the kidney, lungs and uterus. COX-2 is also potently expressed in human colon **cancer** cells, and NSAIDs delay the progress of colon tumors possibly by causing apoptosis of the tumor cells. The risk of developing Alzheimer's disease, which may involve an inflammatory component, is lessened by chronic ingestion of NSAIDs. The new highly selective inhibitors of COX-2 will not only provide a means of delaying premature labor but will also lead to advances in **cancer** therapy and protection against Alzheimer's disease.

L8 ANSWER 7 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998370161 EMBASE
TI [COX 2 inhibitor as drug of many talents?].
COX-2-HEMMER ALS ALLESKONNER?.
AU Wagner U.
SO Pharmazeutische Zeitung, (29 Oct 1998) 143/44 (39-40).
ISSN: 0031-7136 CODEN: PZSED5
CY Germany
DT Journal; Note
FS 002 Physiology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA German
SL German

L8 ANSWER 8 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 1998351229 EMBASE
TI Clinical models of chemoprevention for colon **cancer**.
AU Krishnan K.; Ruffin IV M.T.; Brenner D.E.
CS Dr. K. Krishnan, Department of Internal Medicine, Division of Hematology/Oncology, East Tennessee State University, Johnson City, TN 37614-70622, United States
SO Hematology/Oncology Clinics of North America, (1998) 12/5 (1079-1113).
Refs: 235
ISSN: 0889-8588 CODEN: HCNAEQ
CY United States
DT Journal; General Review
FS 016 Cancer
017 Public Health, Social Medicine and Epidemiology
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Colon **cancer** is a common malignancy in the westernized world and is incurable in its advanced stages. This article summarizes the currently available information on colorectal **cancer** chemoprevention. A brief outline of the incidence and etiologic factors is followed by a discussion of the evidence on which chemopreventive strategies for colon **cancer** are modeled. This includes a description of the development of surrogate endpoint biomarkers and experimental models to study colorectal **cancer** chemopreventives, a review of the promising colorectal **cancer** chemopreventives, and a discussion of the issues to be addressed in the design of future chemoprevention trials. The article concludes with an emphasis on the development and validation of biomarkers and selection of high-risk cohorts using genetic and epidemiologic tools as the main goals of future colon **cancer** chemoprevention trials before large-scale, risk-reduction trials are conducted.

L8 ANSWER 9 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 1998203476 EMBASE
TI **Cancer** and arthritis share underlying processes.
AU Ziegler J.
SO Journal of the National Cancer Institute, (3 Jun 1998) 90/11 (802-803).
ISSN: 0027-8874 CODEN: JNCIAM
CY United Kingdom
DT Journal; Note
FS 016 Cancer
037 Drug Literature Index
LA English

L8 ANSWER 10 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 1998195193 EMBASE
TI Building better aspirin: Does aspirin ward off **cancer** and Alzheimer's?.
AU Pennisi E.
SO Science, (22 May 1998) 280/5367 (1191-1192).
ISSN: 0036-8075 CODEN: SCIEAS
CY United States
DT Journal; Note
FS 036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LA English
SL English
AB New aspirin-like compounds target a single enzyme to deliver pain relief without stomach and kidney damage. They may also slow the development of

**cancer** and Alzheimers's disease.

L8 ANSWER 11 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998168912 EMBASE
TI Cyclooxygenases 1 and 2.
AU Vane J.R.; Bakhle Y.S.; Botting R.M.
CS J.R. Vane, William Harvey Research Institute, St Barth./Royal Lon. Sch. Med./Dent., Queen Mary and Westfield College, Charterhouse Square, London EC1M 6BQ, United Kingdom
SO Annual Review of Pharmacology and Toxicology, (1998) 38/- (97-120).
Refs: 127
ISSN: 0066-4251 CODEN: ARPTDI
CY United States
DT Journal; General Review
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Cyclooxygenase (COX), first purified in 1976 and cloned in 1988, is the key enzyme in the synthesis of prostaglandins (PGs) from arachidonic acid. In 1991, several laboratories identified a product from a second gene with COX activity and called it COX-2. However, COX-2 was inducible, and the inducing stimuli included pro-inflammatory cytokines and growth factors, implying a role for COX-2 in both inflammation and control of cell growth. The two isoforms of COX are almost identical in structure but have important differences in substrate and inhibitor selectivity and in their intracellular locations. Protective PGs, which preserve the integrity of the stomach lining and maintain normal renal function in a compromised kidney, are synthesized by COX-1. In addition to the induction of COX-2 in inflammatory lesions, it is present constitutively in the brain and spinal cord, where it may be involved in nerve transmission, particularly that for pain and fever. PGs made by COX-2 are also important in ovulation and in the birth process. The discovery of COX-2 has made possible the design of drugs that reduce inflammation without removing the protective PGs in the stomach and kidney made by COX-1. These highly selective COX-2 inhibitors may not only be anti- inflammatory but may also be active in colon **cancer** and Alzheimer's disease.

L8 ANSWER 12 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998155426 EMBASE
TI COX-2 inhibitors for colorectal **cancer**.
AU Elder D.J.E.; Paraskeva C.
CS C. Paraskeva, Dept. of Pathology and Microbiology, University of Bristol, Bristol BS8 1TD, United Kingdom. C.Paraskeva@bristol.ac.uk
SO Nature Medicine, (1998) 4/4 (392-393).
Refs: 11
ISSN: 1078-8956 CODEN: NAMEFI
CY United States
DT Journal; Note
FS 016 Cancer
037 Drug Literature Index
048 Gastroenterology
LA English

L8 ANSWER 13 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998130236 EMBASE
TI Opportunities in pain therapy: Beyond the opioids and NSAIDs.
AU Kowaluk E.A.; Arneric S.P.; Williams M.
CS M. Williams, Neurological Diseases Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-3500, United States. mike.williams@abbott.com
SO Emerging Drugs, (1998) 3/- (1-37).
Refs: 77
ISSN: 1361-9195 CODEN: EMDRFV

CY United Kingdom
DT Journal; General Review
FS 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Pain remains a major factor in patients seeking physician assistance. Neither the NSAIDs (non-steroidal, anti-inflammatory drugs) nor the opioids represent a complete answer to pain control, either alone or in combination. Recent research advances using molecular biological techniques have established that pain is a complex process involving multiple neurotransmitter/neuromodulator targets in the spinal cord, in ascending and descending spinal pathways and in the central nervous system as well as receptors and enzymes that are induced as part of the pain process. These advances, coupled with the considerable unmet medical need in the area of analgesics, are anticipated to lead to novel, non-opioid, non-NSAID approaches to pain relief and control.

L8 ANSWER 14 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998129411 EMBASE
TI Drug currently in phase III trials for arthritis shows tumor-inhibiting potential in colon **cancer** model.
SO ONCOLOGY, (1998) 12/3 (423).
ISSN: 0890-9091 CODEN: OCLGE
CY United States
DT Journal; Note
FS 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LA English

L8 ANSWER 15 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 97101463 EMBASE
DN 1997101463
TI Cyclo-oxygenase isoenzymes. How recent findings affect thinking about nonsteroidal anti-inflammatory drugs.
AU Jouzeau J.-Y.; Terlain B.; Abid A.; Nedelec E.; Netter P.
CS Dr. P. Netter, Faculte de Medecine, Laboratoire de Pharmacologie, Boite Postale 184, 54505 Vandoeuvre les Nancy, France
SO Drugs, (1997) 53/4 (563-582).
Refs: 238
ISSN: 0012-6667 CODEN: DRUGAY
CY New Zealand
DT Journal; General Review
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The discovery of at least 2 cyclo-oxygenase (COX) isoenzymes, referred to as COX-1 and COX-2, has updated our knowledge of nonsteroidal anti-inflammatory drugs (NSAIDs). This has lead investigators to reconsider what can be awaited from this class of drugs. The 2 COX isoenzymes share structural and enzymatic similarities, but are specifically regulated at the molecular level and may be distinguished apart in their functions, although some physiological overlap between them does occur. The major goal in developing selective COX inhibitors is to improve NSAID tolerability. Classic NSAIDs preferentially inhibit COX-1 in vitro, but it appears hazardous to judge their gastrointestinal (GI) safety profile from these data. New compounds with a high selectivity for COX-2, especially those that are non-acidic, may be better tolerated in the GI tract. While these compounds also might have a potential use in various diseases such as colorectal **cancer** and neurodegenerative

diseases of the Alzheimer type, the possible appearance of adverse effects, perhaps renally-related, must be taken into consideration. Finally, well-designed large clinical trials are required to adequately estimate both the promising therapeutic advantages that may be offered by highly selective NSAIDs, and the potential drawbacks that may be inherent with prolonged COX-2 inhibition.

L8 ANSWER 16 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 97093441 EMBASE
DN 1997093441
TI **Cancer** pain treatment insights.
AU Barkin R.L.
CS R.L. Barkin, 1653 West Congress Parkway, Chicago, IL 60612-3864, United States
SO Pharmacotherapy, (1997) 17/2 (397-398).
Refs: 7
ISSN: 0277-0008 CODEN: PHPYDQ
CY United States
DT Journal; General Review
FS 024 Anesthesiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English

L8 ANSWER 17 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 96310572 EMBASE
DN 1996310572
TI Evaluation of cyclooxygenase-2 inhibitor for potential chemopreventive properties in colon carcinogenesis.
AU Reddy B.S.; Rao C.V.; Seibert K.
CS American Health Foundation, One Dana Road,Valhalla, NY 10595, United States
SO Cancer Research, (1996) 56/20 (4566-4569).
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB Epidemiological and laboratory studies indicate an inverse relationship between the risk of colon **cancer** development and intake of nonsteroidal antiinflammatory agents, including aspirin. One of the mechanisms by which nonsteroidal antiinflammatory agents inhibit colon carcinogenesis is through the inhibition of prostaglandin production by cyclooxygenase isozymes (COX-1 and COX-2). Overexpression of COX-2 has been observed in colon tumors. Thus, selective inhibitors of COX-2 could potentially serve as chemopreventive agents. We have assessed the chemopreventive properties of SC-58635, a COX-2 inhibitor, and of sulindac, as a positive control, in a double-blind study, using azoxymethane-induced colonic aberrant crypt foci (ACF) as a measure of efficacy. Five-week-old male F344 rats were fed the control diet (modified AIN-76A) or experimental diets containing 150 or 1500 ppm SC-58635, 320 ppm sulindac, or 1500 ppm placebo. Two weeks later, all animals except those in vehicle (normal saline)-treated groups were s.c. injected with azoxymethane (15 mg/kg of body weight, once weekly for 2 weeks). At 16 weeks of age, all rats were sacrificed and colons were evaluated for ACF. As expected, dietary administration of sulindac suppressed ACF development as such and reduced crypt multiplicity in terms of number of aberrant crypts/focus. Administration of 1500 ppm SC-58635 inhibited total ACF induction and crypt multiplicity by about 40-49%. Our finding that SC-58635 significantly suppressed colonic ACF formation and crypt multiplicity strengthens the hypothesis that a selective COX-2 inhibitor possesses chemopreventive activity against colon carcinogenesis.